Early Journal Content on JSTOR, Free to Anyone in the World

This article is one of nearly 500,000 scholarly works digitized and made freely available to everyone in the world by JSTOR.

Known as the Early Journal Content, this set of works include research articles, news, letters, and other writings published in more than 200 of the oldest leading academic journals. The works date from the mid-seventeenth to the early twentieth centuries.

We encourage people to read and share the Early Journal Content openly and to tell others that this resource exists. People may post this content online or redistribute in any way for non-commercial purposes.

Read more about Early Journal Content at http://about.jstor.org/participate-jstor/individuals/early-journal-content.

JSTOR is a digital library of academic journals, books, and primary source objects. JSTOR helps people discover, use, and build upon a wide range of content through a powerful research and teaching platform, and preserves this content for future generations. JSTOR is part of ITHAKA, a not-for-profit organization that also includes Ithaka S+R and Portico. For more information about JSTOR, please contact support@jstor.org.

THE CAUSATION OF GASTRIC AND DUODENAL ULCER BY STREPTOCOCCI *

PLATES 5 TO 14

EDWARD C. ROSENOW

From the Memorial Institute for Infectious Diseases, Chicago, and the Mayo Foundation, Rochester, Minnesota

Lesions of the stomach have been produced experimentally by excision; by tying a fold of mucous membrane with a string; by local application of the cautery, and of corrosive chemicals, such as silver nitrate and nitric acid;[1] by the introduction of very hot gruels;[2] by the submucous injection of silver nitrate,[3] nitric acid, adrenalin, alcohol.[4] and gastro-toxic serum;[5] and by the injection of lead chromate[6] and fat[7] into the gastric artery; but since these lesions heal promptly in from 5 to 21 days, according to their severity,[1,2,6] and since the methods used are so foreign to what could occur, valuable tho the results are in one respect or another, they have little bearing on the problem of ulcer of the stomach as it occurs in man.

The hemorrhages, erosions, and ulcerations observed during severe intoxication following systemic injections of snake venom, pilocarpin, atropin, chloroform, phenol, copper sulfate,[8] bile, and bile salts,[9, 10] B-tetra-hydronaphthylamine,[11] adrenalin,[12] diphtheria toxin,[13, 14] and culture filtrates of various bacteria, while having some parallelism in acute ulcer during severe or fatal intoxications or infections, have little bearing on the problem of the usual ulcer of the stomach in man.

The same may be said of the lesions of the stomach which develop commonly in animals during the moribund condition following adrenalectomy.[15, 16, 17, 18, 19, 20]

Ulcer of the stomach has been produced by interference with its nerve supply (hence the blood supply), by section either of the vagus or of the sympathetic nerves, or of both, and by section of the spinal cord.[21, 22, 23, 24] Most observers, however, have obtained only doubtful results in this field. The studies of Vedova[22] and Durante[23] merit special mention. They have shown that in dogs and rabbits ligation or section of the sympathetic nerves is followed somewhat regularly by acute ulcer of the stomach. In some instances they have observed ulcers which were chronic in type, but not in time, the animals surviv-

* Received for publication March 28, 1916.

ing the operation for a short time only. The lesions in the stomach were due according to Durante to spasm of the blood vessels as the result of an over-production of adrenalin, the adrenals showing marked congestion and hemorrhage following ligation of the splanchnic nerves. But since there is no evidence of increased adrenal function, as manifested especially by an increased blood pressure, in patients with ulcer, and since the death of the animals occurred as a result of the method employed, it is difficult to see how these results, suggestive as they are, can be applied, for in ulcer the interference with the nerve supply of the stomach is necessarily slight.

The infectious origin of ulcer, while not generally accepted, has had adherents for many years. Experimentally, ulcer has been produced by intravenous injections of the pyocyaneus bacillus,[25] the dysentery bacillus,[26] the lactic-acid bacillus,[27] and the colon bacillus.[28, 29, 30]

Ulcer was found to occur as a part of a general pyemia following intravenous injections (1) of pus by Lebert[31] (1857) and by Cohn[32] (1860), (2) of streptococci and staphylococci by Letulle,[33] and (3) of pneumococci by Bezançon and Griffon.[34] It is a well-known fact that ulcer of the stomach in man occurs not infrequently during severe or fatal infections of various kinds, particularly streptococcal infections.[35, 36, 5] Bacteria have been repeatedly demonstrated in the edges and floors of ulcers—Boetcher[37] in 1874 being the first to do this—but these have usually been considered secondary invaders. Dudgeon and Sargent[38] isolated a diplostreptococcus from the edges of the ulcers and from the peritoneal exudate in 4 of 9 cases of peritonitis following perforation. The peritonitis was of a mild grade corresponding to the low virulence of the strains isolated. Hutyra and Marek[39] state that ulcer of the stomach is found in domestic animals dead from "catarrhal fever," and in purpura hemorrhagica. Bolton[5] states that probably the commonest cause of necrosis of the mucous membrane and resulting acute ulcer of the stomach is bacterial infection, that the infection occurs through the blood stream, and that the necrosis is due to the direct effect upon the tissues of the bacterial poison, alone or together with the gastric juice. Letulle reports a case of ulcer following chronic abscess of the maxillary antrum, and notes the occurrence of acute ulcer in other cases in which there were local septic foci. This raises the important question, to quote Bolton, "whether many cases of simple acute ulcers owe their origin to some local septic focus which is so commonly unrecognized or unheeded." Recently numerous

observers have emphasized the etiologic relation of focal infection to ulcer of the stomach.

In 1913, I reported[40] some experiments which showed that streptococci, quite irrespective of their original source, when of a certain grade of virulence, exhibit affinity for the gastric mucous membrane, producing a localized infection and ulcer. The report at that time was summarized as follows:

> Intravenous injection of streptococci of the proper grade of virulence may be followed by ulcer of the stomach and duodenum. The ulceration is due to a localized infection and secondary digestion. The ulcers are usually single and deep with marked tendency to hemorrhage and perforation, and in many respects resemble gastric ulcer in man. When we take into consideration this close resemblance, that injection of streptococci which have grown in tonsils produce the lesions, and that the virulence of the germs when the affinity for the stomach is greatest, is of such a character that a general infection does not occur, it appears altogether reasonable to suppose that in man gastric ulcer may be caused by streptococci also. The supposed relation between infected tonsils or gums and gastric ulcer may be due not to the swallowing of bacteria, as usually supposed, but to the entrance into the blood of streptococci of the proper kind of virulence to produce a local infection in the wall of the stomach. Many other observations might be cited, such as associated infections of the gall bladder and appendix, which suggest that gastric ulcer may be due to streptococci.

Before it could be accepted, however, that the usual ulcer of the stomach in man is due commonly to a local hematogenous streptococcal infection, it was necessary to show, first, that in this type of ulcer, these organisms are commonly present to the exclusion of other bacteria; and second, that the streptococci isolated from the ulcer wall, as well as those from foci of infection in patients having ulcer, produce, when injected into animals under otherwise normal conditions, ulcers of the stomach and of the duodenum resembling those in man.

By the use of a special technic the first requirement has been covered, and reported.[41] Streptococci have been demonstrated in the tissue or isolated in cultures (often in pure form) in 42 of 54 typical chronic ulcers in man. The second requirement, as I have pointed out recently,[42] has also been fulfilled. I wish now to give in greater detail the results of my experiments.

TECHNIC

The technic of making cultures from ulcer is described in another paper.[41] In collecting material for cultures, great effort was made to obtain bacteria from the depths of the foci of infection with as little surface contamination as possible. This is of great importance. The bacteria for injection were grown in tall columns (12 cm.) of ascites dextrose broth at 35-37 C., for from

18 to 24 hours, centrifugated, the clear broth poured off, and the bacteria suspended in salt solution so that 1 c.c. of the suspension contained the growth from 15 c.c. of the broth culture. Blood-agar-plate cultures and smears were made of the material obtained directly from the ulcer or the focus, from the broth cultures, and from the suspensions immediately before injection, to determine the viability and identity of the organisms present.

In some instances, small doses of the broth culture and cultures from blood-agar slants were injected. Bacteria from the ulcers, when injected into animals, were usually in the second culture, from single colonies (from 2 to 78 days old) in the original shake cultures. In the case of strains from foci of infection, the bacteria used for injection were usually from the primary culture, from 18 to 48 hours after the inoculation of material from the focus directly into tall columns of ascites dextrose broth. The broth culture filtrates were injected in some instances to determine the presence or absence of an ultramicroscopic virus. They showed only slightly greater tendency to produce lesions in the stomach than did filtrates from other streptococcus cultures.

Routine cultures were made in the case of the animals from the blood (0.5 c.c.), the joint fluid (usually from 2 or more joints), the bile and from emulsions of the ulcers, of the areas of hemorrhage, and often from the adjoining normal mucous membrane. Cultures from various other tissues and from the blood at intervals during life, were made in selected instances. The technic for tissue cultures from animals was similar to that employed in making cultures from ulcers from patients.

No special attention was paid to the diet of the animals. The injections were made usually in the latter part of the day, some hours after the feeding period. Except for feeding experiments, and the local and intraperitoneal injections of the streptococci, the bacteria were injected intravenously, the injections being made rather rapidly through a fair-sized needle (23 gage). It was the rule to inject at least 2 animals with a given strain, one receiving a small dose, the other a larger dose. Because of the low virulence of the strains, the dose was relatively large, consisting in the main (for rabbits and dogs) of the growth from 5 to 25 c.c. of the broth culture per kilo of weight. In special instances much smaller doses sufficed to produce ulcer.

For sections the tissues from the ulcers in man and from experimental ulcers were fixed in 10% formalin or in Zenker's fluid, imbedded in paraffin, and stained chiefly with hematoxylin and eosin, methylene blue and eosin, or with neutral gentian. Gram-Weigert's method was used as a routine for the staining of bacteria, care being exercised not to decolorize the sections further than to a pale blue.

REVIEW OF CASES AND EXPERIMENTS

CASE 773

A man, 53 years of age, with typical symptoms of duodenal ulcer of 3 years' duration was operated on by Dr. Bevan Oct. 27, 1913. There was excised a hard, indurated, much thickened and adherent duodenal ulcer, which was perforating against the gall-bladder. Cultures were made at once. Smears from the emulsion showed a few gram-staining cocci and diplococci. The cultures yielded fully 1,500 colonies of staphylococci and approximately 20 colonies of a short-chained nonhemolyzing nonadherent streptococcus.

The streptococcus (Fig. 1) as isolated, was injected into 2 dogs and 2 rabbits. The dog receiving the large dose died in 48 hours, showing marked

distention of the stomach with gas containing a large amount of carbon dioxid and hemorrhages of the mucous membrane of the stomach with ulceration in two areas. The other dog, 13 weeks later, died of distemper. It showed one round deep sharply circumscribed, somewhat indurated ulcer of the duodenum, 5 mm. in diameter, 2 cm. beyond the pyloric ring (Fig. 7). The floor of the ulcer in the center consisted only of the thickened and adherent peritoneal coat. No other lesions could be made out. One rabbit developed one ulcer in the pylorus, together with myositis and beginning endocarditis. The other did not show lesions of the stomach, but showed a focal nephritis and myocarditis.

The staphylococci failed to produce lesions of the stomach, but produced a focal nephritis, and, in one rabbit, cholecystitis.

The feeding of a large amount of cultures of these strains mixed with chopped meat and particles of dried splintered bone, failed to produce lesions in the stomach or duodenum in the 3 dogs so treated.

After 1 animal passage, the streptococcus produced acute ulceration of the stomach in a rabbit, and a chronic ulcer causing death from hemorrhage in the only dog injected (see report for Dog 41).

After 2 animal passages, the streptococcus was injected into 2 dogs. One developed 3 hemorrhagic ulcers—2 in the duodenum and 1 in the pyloric end of the stomach—cholecystitis, pancreatitis with fat necrosis, enteritis, and myocarditis. The other dog developed no lesions of the stomach or duodenum, but showed fatty degeneration of the liver and ulcerative colitis.

After 3 animal passages, the streptococcus produced 2 ulcers of the stomach in one of 2 dogs injected, together with enteritis and colitis, and intussusception of the ileum into the cecum. Cultures from the blood of these dogs yielded both nonhemolyzing and hemolyzing streptococci. The nonhemolyzing strain in the next passage produced no lesions of the stomach in the 3 rabbits injected, one rabbit developing arthritis, and another cholecystitis; the hemolyzing strain likewise produced no lesions of the stomach, and caused a suppurative arthritis in 2 rabbits and 1 dog. The dog showed what appeared to be a phlegmonous gastritis, but no ulceration.

After 5 animal passages, the nonhemolyzing strain was injected into 3 guinea-pigs, 2 dogs, and 1 rabbit. All but 2 of these animals showed hemorrhages in the lungs. The rabbit and the dogs showed hemorrhages of the gall-bladder and mild arthritis. In 1 dog there was marked degeneration of the liver. Cultures from the joint fluid in these were negative. Cultures from the livers which showed no gross changes, remained sterile, while those from the liver in which there was degeneration, yielded a large number of streptococci.

Dog 41.—Injected Nov. 11, 1914, with the growth from 150 c.c. of a dextrose-broth culture of the streptococcus after one animal passage. Cultures from the blood the day after injection were negative.

Nov. 25.—Dog seemed well, but had lost in weight, and was less active than usual.

Jan. 3.—Died at 9:00 a. m., 53 days after a single injection. Emaciation; tissues everywhere pale, hemoglobin 30%; blood remained unclotted for 30 minutes. There were one small round deep ulcer with elevated and indurated margins and hemorrhagic base, which extended through the mucous membrane; one healing ulcer in the stomach and one in the duodenum; and one active infected ulcer 1 cm. beyond the pyloric ring (2 by 5 mm.). The margins ot the latter were infiltrated and opaque, and the peritoneum opposite showed

thickening and adhesions. The liver disclosed fatty infiltration and localized fibrous myocarditis. The other organs revealed no changes. A Weber test for occult blood in the dark brown contents of the lower bowel was strongly positive.

Cultures from blood, joint fluid, and kidney remained sterile, while those from bile yielded 15 colonies of nonhemolyzing streptococci.

Dog 37.—Injected intravenously Nov. 3, 1913, with the growth from 280 c.c. of a dextrose-broth culture of the streptococcus in its second culture.

Nov. 7.—Cultures from blood gave the streptococcus injected.

Nov. 16.—Growth from 120 c.c. injected intravenously.

Nov. 19.—Culture from blood made the day after injection yielded streptococci.

Nov. 28.—The dog had grown thin, did not eat with a relish, but otherwise seemed fairly well.

Feb. 13.—Found dead from distemper. There was an acute pneumonia with pleuritis. The stomach was normal—no scars indicating healed ulcers could be made out. In the duodenum, 2 cm. from the pyloric ring, there was a round deep sharply circumscribed ulcer, 5 mm. in diameter (Fig. 7). The margins were undermined and adherent to the muscular layer. The floor in the center consisted of the thickened and adherent peritoneal coat.

Sections showed marked invasion of the muscular coat by connective tissue, and thickening of the peritoneal coat (Fig. 8, a and b). The mucous membrane at the margin of the ulcer revealed round-cell infiltration in areas at the junction of the uninvolved portion. The mucous glands evinced little change. No thrombosed blood vessels could be made out. A search for bacteria revealed a few diplococci (Fig. 9).

CASE 779

Chronic ulcer of the stomach in a woman 43 years of age. The symptoms of ulcer had been present for 12 years. She had had the usual periodic attacks of exacerbation and remissions, and was finally operated on by Dr. Ochsner Oct. 29, 1913. There was an indurated crater-like ulcer, 3 cm. by 1 cm., at the pyloric end of the stomach. The pylorus and the lymph gland draining the area were removed and cultured. The margin and base of the ulcer were indurated, the base clean and smooth. The mucous membrane was adherent and not undermined. The ulcer appeared to be healing.

Smears from the base of the ulcer showed leukocytes, epithelial cells, yeast cells, and gram-positive cocci, mostly within leukocytes.

Oct. 30.—Cultures from emulsion of the ulcer, made after the surface was sterilized, yielded approximately 180 colonies of small cocci, which appeared singly and in masses, and approximately 50 colonies of a short-chain streptococcus, while those from the lymph gland gave 5 colonies of the streptococcus. Control cultures from the adjacent normal mucous membrane were negative except for a few colonies of staphylococci and aerobic saprophytic bacilli.

Nov. 4.—Subcultures of 8 colonies of the small gram-positive streptococcus from the ulcer and of 3 of those from the node, yielded small grayish nonhemolyzing nonadherent colonies on blood-agar plates, and short chains in ascites dextrose broth identical with those found in Case 773 (Fig. 1).

The streptococcus in second culture was injected into 1 rabbit and 1 dog. The mucous membrane of the rabbit did not show lesions at the end of 1 week, while that of the dog, 4 months after the injection, showed a scar indi-

cating a healed ulcer near the pyloric ring. After the streptococcus had undergone 1 animal passage, the following experiment was made.

Dog 42.—Injected intravenously, Nov. 7, with the growth from 150 c.c. of an ascites-dextrose-broth culture of the streptococcus isolated from the blood of the dog mentioned.

Nov. 8.—Ill, lay quiet, did not eat. There was no tenderness or swelling of the joints.

Nov. 11.—Ill. Chloroformed, and examined at once. In the stomach there were numerous small (1 to 5 mm.) and large (1 to 3 cm.) hemorrhagic areas, areas of necrosis, erosions, and ulcerations (Fig. 3). The lesions were more numerous in the fundus, but larger in the pylorus. The intervening mucous membrane, except for slight congestion, was normal, as was that of the duodenum. The stomach contents, free from food, were strongly acid in reaction and contained a small amount of altered blood. The mucous membrane of the small and large intestines was congested.

Sections through two areas of hemorrhage and ulceration in the cardiac end of the stomach showed marked extravasation of blood, which was most marked as the surface of the mucous membrane was reached. This was true in practically all the areas of hemorrhage. In one there was distinct ulceration. The ulcerated area was covered in places by a thick layer of necrotic cells, numerous leukocytes, blood corpuscles, and fibrin. The mucous membrane beneath this layer presented an interesting picture. There were, first, a dense layer of polymorphonuclear leukocytes, then a layer in which there was marked hemorrhage with less leukocytic infiltration, and then the more normal gland structure, throughout which were found leukocytes in large number (Fig. 4). The chief cells showed marked degeneration; the protoplasm was granular, the nuclei fragmented, with marked desquamation. The eosin-staining parietal cells, on the other hand, appeared normal, even where all the chief cells had disintegrated and desquamated. Some of these retained normal staining properties and position, even where they had been detached from the acini (Fig. 5). The other coats were unchanged. The blood vessels in the submucosa were dilated and a number of veins showed rather marked mural implantation of leukocytes, appearing as a beginning thrombosis (Fig. 4). Search for bacteria revealed few diplococci in the deeper layers, but masses of diplococci and short chains beneath the sloughing necrotic layers, as is well shown in Fig. 6. On the surface were a few large gram-staining bacilli, but none in the deeper layers.

After 2 animal passages the streptococcus was injected into 3 rabbits and 1 dog. One rabbit died in 24 hours with streptococcemia, hemorrhage in the septum of the heart, and acute splenitis, but without lesions in the stomach. The other two died in 4 and 18 days. The one dying in 4 days showed multiple arthritis, the other arthritis of the right knee, and a healing ulcer (5 by 3 mm.) in the cardiac end of the stomach. The dog which died in 18 days had developed 2 healed ulcers of the cardiac end of the stomach, a local nephritis, fatty degeneration of the liver, and localized myocarditis.

After 3 animal passages the streptococcus was injected into 1 dog, which died from an overwhelming infection in 24 hours. The staphylococcus was repeatedly injected intravenously into 2 rabbits, neither of which developed lesions of the stomach. Mixtures of the cultures of the staphylococcus and the streptococcus fed with chopped meat and sharp particles of dried splintered bone to 2 dogs, did not produce lesions.

CASE B

Ulcer of the stomach in a woman 28 years of age, whose symptoms had existed for 5 years. This ulcer, which was 3 cm. from the pyloric ring, was adherent to the duodenum and the pancreas, causing hour-glass constriction.

The usual streptococcus was isolated in pure culture, and injected as soon as sufficient growth could be obtained, into 2 rabbits and 3 dogs of medium size.

The rabbits died in 24 hours. They were examined immediately. Both disclosed marked, but localized, hemorrhages of the stomach with gaseous distention. One showed, in addition, hemorrhages in the pericardium and in the aortic valve, while the other showed small hemorrhages in the tricuspid valve. Cultures from emulsions of the hemorrhagic areas in the stomach yielded many streptococci; those from the blood, a smaller number.

All 3 dogs had developed lesions of the stomach. The one which had received the largest dose died in 24 hours, showing acute dilatation of the stomach, with circumscribed hemorrhages in the cardiac end, a large amount of brownish fluid, no food, and gaseous distention. The gas in the stomach of the dog, as in both the rabbits, contained large amounts of carbon dioxid. There were, in addition, hemorrhages of the mucous membrane of the colon. Another dog died in 48 hours, with one acute ulcer of the fundus extending through the mucous membrane, numerous small punctate hemorrhages, some of which showed beginning ulceration, and numerous small and occasionally white necrotic areas in the mucous membrane of the large intestine. The third dog, chloroformed 8 days after injection, had developed a small round ulcer (5 mm. in diameter) of the pylorus, 2.5 cm. from the pyloric ring. Cultures from the blood were sterile, while those from the ulcer gave a moderate number of nonhemolyzing streptococci.

The strain isolated from the dog which died in 4 hours (1 animal passage) was injected into 2 rabbits and 2 cats. One rabbit died in 2 days, the other in 13 days. The former showed hemorrhage in the tricuspid valve with a beginning endocarditis, the latter what appeared as a phlegmonous gastritis, cholecystitis, medullar nephritis and pyelitis, and endocarditis. Cultures from the mucous membrane of the second rabbit yielded a large number of streptococci and a few colonies of colon bacilli. The blood was sterile.

The cat which had received the large dose showed after 24 hours marked gaseous (carbon dioxid) distention of the stomach, extensive hemorrhage of the mucous membrane of the fundus, and a moderate amount of chocolate-colored blood. Cultures from the blood gave 20 colonies; from the spleen, 40; two areas of hemorrhage in the mucous membrane yielded 2,000 and 3,000 colonies, and the adjacent normal mucous membrane, 40 colonies of the nonhemolyzing streptococcus.

The cat which had received the smaller dose seemed ill, ate poorly, and lost in weight for a number of weeks, then regained weight and became apparently perfectly well. It was chloroformed 14 weeks after injection. No lesions were found except a scar (0.5 cm. in diameter) in the mucous membrane of the stomach, 2 cm. from the pyloric ring.

CASE 885

Chronic ulcer of the stomach with perforation. An emergency operation was performed Jan. 31, 1914, by Dr. Hirst. There were a perforating ulcer of the stomach and a beginning peritonitis. The ulcer was excised and the area inverted. The patient recovered.

Cultures yielded approximately 5,000 colonies of the usual nonhemolyzing streptococcus and a few colonies of staphylococci and sarcinae.

Dog 65.—Injected intravenously, Feb. 4, with the growth from 150 c.c. of an ascites dextrose broth of the streptococcus in its second culture.

Feb. 14.—Seemed ill, ate little, and had lost in weight.

Feb. 22.—Found dead. Stomach was distended with gas rich in carbon dioxid. It contained a small amount of brown blood-tinged fluid, but no food. A number of small deep ulcers were found in the fundus. In two of these, the inflammation extended through to the peritoneal coat, which was opaque and hyperemic. The mucous membrane of the pylorus was normal. The duodenum showed one large ulcer (1 by 2.5 cm.). The peritoneal coat here was adherent to the surrounding structures and formed the floor of the ulcer.

Sections through one of the ulcers in the stomach revealed leukocytic infiltration in the margin and in the peritoneal and subperitoneal layers, and a moderate number of diplococci. The muscular coat, however, was quite free from infiltration.

CASE 52

Ulcer of the stomach and duodenum in a woman 62 years of age. The patient had had for years severe attacks of migraine. Three years previously she had had a severe attack of herpes zoster, involving the left thorax, and 2 years previously there had been a recurrence of severe pain in the zoster area, but no blistering. One year later she had had two severe hemorrhages from the stomach, but had made a good recovery under medical management, and was again quite free from gastric symptoms. At this time marked tartar deposit was found about the teeth, and marked gingivitis, especially at the outer aspect of the second right lower molar. The patient was advised to have her teeth put in order, but this was not done.

On Aug. 19, 1914, she began vomiting large quantities of blood on two occasions several weeks after an attack of so-called grippe. Three days after the hemorrhages from the stomach, the temperature rose. Altho there were no physical indications of pneumonia or other demonstrable cause, a high fever continued until death occurred.

Only a partial postmortem examination was made. The heart showed chronic mitral endocarditis. The lungs were edematous, but there was no pneumonia. The wall of the duodenum just beyond the pylorus showed two thickened puckered areas, which produced a marked sacculation on the anterior wall, approximately 2.5 cm. in diameter. On opening the stomach, there were found approximately 100 c.c. of mucopurulent material, free from food. The puckered areas in the duodenum were scars of healed ulcers. Just outside of the pyloric ring on the posterior wall, there was an indurated, partially healed ulcer, 0.4 by 1 cm., having a hemorrhagic base. In the pyloric third of the stomach, there were an entirely healed ulcer, and one acute ulcer having a hemorrhagic base, which was not thickened. The mucous membrane of the entire stomach was hyperemic, in places edematous, and studded with numerous punctate hemorrhages, the membrane over some of the hemorrhagic areas being eroded. The mucous membrane adjacent to the ulcer was no more hyperemic than the rest. The lymph glands in the gastro-colic omentum were enlarged and hemorrhagic on the cut surface. No thrombosed blood vessels in the stomach could be found. The gall-bladder was distended with a dark bile, the ducts patent. No gall-stones. The liver showed marked granular and fatty degeneration.

The stomach contents did not have an acid odor and were only slightly acid to litmus. No peritonitis.

Cultures were made from the blood, lymph gland, liver, duodenal contents, duodenal and gastric ulcers, and from pus obtained from the depths of the inflamed gum covering the deposit of tartar on the right lower molar.

Aug. 31.—Cultures in ascites dextrose broth from the gum gave a pure culture of a short-chained streptococcus (Fig. 2); those from the duodenal contents, the emulsion of the ulcers, the blood, the lymph gland, and the liver, gave streptococci and colon bacilli. Ascites-dextrose-agar shake cultures from the ulcer emulsion yielded approximately 6,000 colonies of streptococci, and approximately 150 colonies of colon bacilli. The material withdrawn with a pipet from the margin of the duodenal ulcer—the surface having first been seared—showed mostly streptococci, but also a few colon bacilli.

Sections of the ulcer in the duodenum and of that in the stomach disclosed hemorrhage and leukocytic infiltration of the margin and base, extending through the entire thickness of the mucosa and submucosa. The muscular coat was largely replaced by connective tissue in the case of the duodenal ulcer, but not in the case of the gastric; in the latter was marked leukocytic infiltration of the peritoneal coat, but no perforation. Sections through one of the edematous and hemorrhagic areas revealed marked dilatation of the intraglandular blood vessels, hemorrhage, and leukocytic infiltration. Gram-Weigert stains of sections of the ulcers disclosed numerous streptococci in the margins and bases of the ulcers, and in the peritoneal coat. Those of the edematous areas also showed a number of streptococci. On the surface of the ulcers, as of the hemorrhagic areas, there were found scattered bacilli.

The streptococcus from the tooth was injected, in the first culture, into 4 animals. Of these, all but one showed hemorrhage or ulcer of the stomach. The results in the case of the dog are given in the following.

Dog 120.—Injected intravenously Sept. 1, 1914, with the growth from 150 c.c. of ascites dextrose broth of the streptococcus from the tooth.

Sept. 3.—Dog seemed well. Chloroformed. The mucous membrane of the pyloric end of the stomach was studded with numerous small punctate hemorrhages. There were present a number of larger hemorrhages and 4 ulcers, from 2 to 4 mm. in diameter, near the junction of the middle and lower thirds of the stomach. The intervening mucous membrane was normal. The gastric contents, which had a typical odor, were highly acid in reaction. The gall-bladder, appendix, pancreas, and other organs, appeared normal.

Sept. 4.—Cultures from blood, bile, liver, and joint fluid, sterile. Cultures from the larger ulcer yielded 150 colonies of streptococci, those from the small ulcer 80 colonies, while those from a hemorrhagic area without ulceration of corresponding size, gave approximately 2,400 colonies of the injected streptococci.

The streptococcus from the ulcer was injected, in its second culture, into 12 animals. Of these 8 developed lesions in the stomach, and 5 lesions in the gall-bladder.

After 1 and 2 animal passages, the streptococcus was injected into 6 more animals, giving rise to lesions in the stomach in 1, and to lesions in the gall-bladder in 3.

CASE 112

Single woman, 51 years of age; bookkeeper. She had complained of pain and other symptoms in the epigastrium typical of duodenal ulcer, for 1 year. Pain had been especially severe 6 weeks prior to examination. Aug. 18, 1914,

there were found by Dr. Judd a subacute ulcer of the duodenum, 1 cm. beyond the pylorus, and a chronically inflamed adherent appendix. The overlying and adjacent visceral and parietal peritoneum was very red, loosely adherent, and edematous. The location of the ulcer and the severity of the accompanying inflammation precluded excision of the ulcer. After covering the ulcer with omentum and partially occluding the pylorus, posterior gastro-enterostomy and appendectomy were made. The patient made a prompt recovery.

Sept. 3.—Cultures from the thickened and injected visceral peritoneum overlying the ulcer, gave a moderate number of short-chained nonhemolyzing streptococci and a few colonies of a gram-staining bacillus resembling B. subtilis, while the parietal peritoneum adjacent to the ulcer yielded a few colonies of the same streptococci in pure growth. The sections of the thickened visceral peritoneum showed marked fibrous thickening, perivascular round-cell and leukocytic infiltration, and hemorrhages. Diplococci were found, two of which are shown in Fig. 8.[41]

The streptococcus in its second culture was injected into 4 dogs, 2 rabbits, and 1 guinea-pig, all of which developed ulcer. All the dogs, 1 rabbit, and the guinea-pig developed duodenal ulcer; the other rabbit, ulcer of the stomach and cholecystitis. The dogs, in addition to ulcer of the duodenum, had marked hemorrhages in the stomach and the duodenum. Three of the 4 dogs showed a peritonitis of the lesser peritoneum surrounding the duodenal ulceration. In the dog which developed localized hemorrhages in the gall-bladder, the peritoneal exudate had extended to the gall-bladder and to the under surface of the liver.

After 1 animal passage the strain was injected into 2 dogs. One developed 2 deep hemorrhagic ulcers in the duodenum, hemorrhages of the stomach, marked cholecystitis, localized peritonitis, and hepatitis; the other, cholecystitis and hemorrhages in the duodenum, but no ulcer.

After 2 animal passages the streptococcus was injected into 3 dogs and 2 rabbits. One dog developed an ulcer in the pyloric end of the stomach, endocarditis, and infarcts of the kidney; one, cholecystitis and focal nephritis; the third, ulcer of the stomach and of the duodenum. One rabbit gave ulcer of the stomach, and the other ulcer of the duodenum.

Dog 134.—Injected intravenously, Nov. 4, 1914, 78 days after the original cultures had been made, with the growth from 60 c.c. of an ascites dextrose broth of the streptococcus from the ulcer in Case 112.

Nov. 5.—Found dead. The mucous membrane of the stomach was hyperemic, with numerous small hemorrhages, especially in areas in the pyloric end. The first portion of the duodenum, which was markedly hyperemic, contained three hemorrhagic areas from 5 to 6 cm. in diameter. The mucous membrane in the center of one of these areas just outside the pyloric ring was necrotic and ulcerated. The rest of the mucous membrane of the duodenum and intestine was normal, except for small hemorrhages, especially in the lymph follicles. The peritoneum of the upper portion of the small intestine was hyperemic and opaque, while over the duodenum, gallbladder, and the under surface of the liver, there was a thin layer of loosely adherent fibrinous exudate. The mucous membrane of the gall-bladder was normal. There was a pea-sized hemorrhagic lymph gland adjacent to the duodenum. The mesenteric glands were normal. No other gross lesions.

Nov. 7.—Cultures from the crushed area of hemorrhage in the duodenum yielded fully 10,000 colonies of streptococci, and only 12 colonies of colon bacilli, and the blood a moderate number of gray-producing nonhemolyzing colonies of streptococci. The bile and peritoneal exudate revealed a large number of streptococci in pure growth. The joint fluid was sterile.

Dog 142.—Injected intravenously Sept. 11, 1914, with the growth from 75 c.c. of an ascites-dextrose-broth culture of Strain 112 after 1 animal passage.

Sept. 12.—Dead. There was marked hemorrhage of the cardiac end of the stomach, of the duodenum, and of the small intestines. The gall-bladder was markedly hemorrhagic and edematous, especially over the fundus, where the wall measured from 0.4 to 0.6 cm. The edema was most marked in the submucosa. Mucous membrane swollen, but not ulcerated. Fluid expressed from the wall of the gall-bladder and the surrounding structures, bile-stained. Walls of the cystic and common ducts also edematous. Lymph glands adjacent to the common duct, hemorrhagic. Except for subendocardial hemorrhages, particularly of the left ventricle, no other noteworthy lesions found. Smears from the edematous fluid from the wall of the gall-bladder gave a moderate number of streptococci.

Sept. 13.—Blood-agar-plate cultures of the blood yielded 50, of the bile 2,500, and of the wall of the gall-bladder 8,000 colonies of nonhemolyzing streptococci. The bile showed, in addition, 5 colonies of colon bacilli. Cultures from the bile in tall columns of ascites dextrose agar gave streptococci, gas bacilli, and colon bacilli; from the wall of the gall-bladder, streptococci and gas bacilli, and from the liver, a few colonies of streptococci.

Dog 156.—Injected Sept. 19, 24, and Oct. 2, with the growth from 20, 30, and 40 c.c., respectively, of an ascites dextrose tissue broth of Strain 112, after 2 animal passages.

Oct. 10.—Seemed ill and very weak. Chloroformed, and examined at once. Mucous membrane and tissues everywhere pale, the blood showing only 50% hemoglobin. The stomach, free from food, contained a small amount of brownish material, resembling altered blood. The mucous membrane of the stomach contained approximately 10 small erosions, surrounded by whitish necrotic swollen areas, and a number of small ulcers filled with adherent brownish blood clots. There was one large deep ulcer, 0.6 by 1 cm., in the duodenum just above the ampulla of Vater (Fig. 10). The margin was edematous and necrotic and the base was filled with clotted blood. The liver showed marked fatty degeneration. The lumen of the small and large intestines contained a moderate amount of partially digested blood. No other noteworthy lesions. Smears from the necrotic margin of the ulcer in the duodenum revealed many leukocytes, gram-staining diplococci, and short chains.

Oct. 15.—Cultures from the blood yielded nonhemolyzing streptococci, and from the bile, gas bacilli. Sections through the base of the ulcer showed in the center complete absence of mucous membrane and submucosa, and necrosis of one-third of the circular layer of the muscular coat. There was leukocytic infiltration between the disintegrating epithelial cells in the submucosa, chiefly around vessels, along the connective-tissue stroma, between muscle bundles, and beneath and in the thickened and adherent peritoneal coat. There was no extravasation of red blood corpuscles. The portion of the base of the ulcer which had not yet entirely sloughed, was composed of poorly staining connective-tissue stroma, in which were fragmented cells, leukocytes, thrombosed vessels running at right angles to the floor of the ulcer, and 2 large thrombosed vessels in the submucosa (Fig. 11). The thrombi, which were partially organized,

contained a moderate number of leukocytes. In several sections of a large series studied, there was marked leukocytic infiltration surrounding the thrombosed vessel in the submucosa. Gram-Weigert stains showed a moderate number of diplococci, chiefly in the area of leukocytic infiltration, and a few in one of the thrombi in the small vessels shown in Fig. 12. On the surface of the ulcerated area and the adjacent normal mucous membrane, there were found a few scattered cocci and large bacilli.

CASE 236

Recurring ulcer of the stomach in a young man. I am indebted to Dr. Sippy for this case. The patient had developed typical symptoms of ulcer of the stomach 6 months before, after ulceration of a tooth. He had completely recovered under medical management. Since that time, he had had a discharging sinus, as a result of trouble with the tooth, which alternately healed, formed a blister, and then again discharged pus. There had been a sudden recurrence of the ulcer of the stomach associated with hemorrhage, 5 weeks prior to examination.

On Jan. 22, 1915, two days previous to the extraction of the tooth, a culture was made from pus withdrawn from the sinus after sterilization of the surface and insertion of a pipet for a depth of 1 cm. A blood-agar-plate culture gave an almost pure culture of Streptococcus viridans, with a few colonies of hemolytic streptococci. Ascites-dextrose-broth cultures yielded a pure growth of a short-chained streptococcus. The cultures from the tooth pulp, 2 days later, yielded exactly similar results.

Injection of this strain into guinea-pigs, rabbits, and dogs, showed a most pronounced tendency on the part of the organism to lodge in the mucous membrane of the stomach, producing hemorrhages and ulceration. Intravenous injection of the strain from the sinus was made into 2 rabbits and 1 dog. The dog developed ulcer in the duodenum; one rabbit gave hemorrhage and ulcer of the cardiac end of the stomach, and the other rabbit arthritis, but no lesions of the stomach.

The cultures from one of the ulcers in the dog gave the streptococcus in pure growth in broth and in ascites dextrose agar (17 colonies). The broth culture, injected intravenously into 1 rabbit and 1 guinea-pig, produced hemorrhage or ulcer in both; injected intraperitoneally into 1 rabbit and 1 guinea-pig, it produced in the rabbit an acute ulcer (2 by 3 cm.) in the lesser curvature of the stomach, but no lesions in the guinea-pig; injected intrapleurally into 1 guinea-pig, it caused two small ulcers in the pyloric end of the stomach; injected subcutaneously into 1 guinea-pig, it gave rise to no lesions in the stomach. The streptococcus culture from the tooth was injected intravenously into 1 rabbit and 1 dog, and intraperitoneally into 1 guinea-pig. All developed hemorrhage and ulcer of the stomach or of the duodenum. Cultures from one ulcer from each of 7 animals yielded from 5 to 40 colonies of streptococci, irrespective of whether the injection had been made intravenously, intraperitoneally, or intrapleurally.

CASE 227

An ulcer of the stomach in a physician of middle age. There was a history of severe recurring attacks of tonsillitis and rhinitis for years. On April 21, 1914, during an attack of acute rhinitis and acute indigestion, resembling ulcer, there was isolated a pure culture of a green-producing streptococcus from the mucopurulent discharge from the nose. This was injected into 5 animals. Of

these, 2 developed ulcer of the stomach, 1 hemorrhages of the stomach, and 2 cholecystitis. No particular importance was attached to these findings at that time.

Dec. 19.—The symptoms of gastric ulcer were typical. The tonsils showing marked infection, tonsillectomy was done. Salt-solution suspensions of the extirpated and washed tonsils caused hemorrhage or ulcer of the stomach in 2 rabbits. Cultures from the tonsils, injected into 6 animals, produced hemorrhages or ulcer of the stomach in 4.

After the removal of the tonsils, while the patient was being treated with an autogenous vaccine prepared from the streptococcus isolated from the ulcer in one of the animals, the symptoms of ulcer were reduced for a short time, but they returned, and persisted in spite of strict medical management (Dr. Frick).

Feb. 27.—The teeth showed the presence of a number of pyorrheal pockets. Cultures from the pus from these pockets injected into 1 dog produced hemorrhage and ulcer of the stomach. On the basis of these findings, the involved teeth were extracted on Aug. 15, 1915, the symptoms of ulcer having persisted during the interval. He was then placed on strict medical treatment for ulcer, and has since been free from symptoms and has regained his former weight.

CASE 531

Recurring ulcer of the stomach in a woman 34 years of age (Dr. Plummer). The trouble had begun 8 years before, with recurring attacks of sharp cramp-like pain in the epigastrium. The attacks were usually associated with nausea, in former years with vomiting and numerous hemorrhages from the stomach, and were followed by soreness in the epigastrium. The attacks, which always followed tonsillitis, lasted from 10 to 14 days and were followed by intervals of 3 or 4 months of almost complete relief. Systolic blood pressure 122, temperature 99.2, hemoglobin 70%, urine normal, except for a small amount of albumin. A test meal showed a total acidity of 48, free hydrochloric acid 28, combined acids 20, and no occult blood. An x-ray of the chest and stomach was negative. Tonsils small and only moderately infected. Slight tenderness over the right abdomen, most marked over the right lower quadrant, but no muscle spasm. On account of the apparent etiologic relation between the tonsils and her attacks, tonsillectomy was advised. The extirpated tonsils, which were small, revealed only a moderate grade of infection.

Cultures gave chiefly Streptococcus viridans, a few hemolytic streptococci, and staphylococci. The broth cultures for injection yielded chiefly rather long-chained streptococci.

These cultures were injected intravenously into 2 guinea-pigs and 4 rabbits. All but 1 rabbit and 1 guinea-pig showed either hemorrhage or ulcer, or both, of the stomach or of the duodenum. The rabbit injected with 3 c.c. of the emulsion from the tonsils developed both hemorrhage and ulcer of the stomach. Only 2 of the animals died. The rest seemed well. An ulcer which was cultured, yielded 50 colonies of streptococci in pure growth. Since the tonsillectomy, the patient has gone for a longer interval without gastric attack than at any time during a period of 8 years.

In previous papers,[40, 43] I have pointed out that when strains of streptococci of low virulence are passed successively through animals, their place of localization changes with returning virulence, and that

when these strains reach the stage at which they give rise to muscle lesions, they are apt also to produce ulcer of the stomach and focal nephritis. The following experiment will serve to illustrate these observations:

Dog 25.—Injected intravenously March 20, 1913, with the growth from 240 c.c. of an ascites-dextrose-broth culture of streptococcus ($R51A^{80}$) isolated 11 years previously as a pneumococcus in pneumonia. It had lost practically all virulence years before, had acquired hemolytic properties, and was now in the 20th animal passage.

March 27.—The dog was lame in left front leg.

March 28.—Turbid fluid from both knee joints.

March 29.—Right wrist was swollen and tender; the animal limped, was sensitive over muscles; movements caused pain.

April 8.—Found dead, body warm. Marked pallor of all tissues; hemoglobin 40%. Moderate amount of altered blood in stomach. There were one large ulcer (1 by 3 cm.) in the duodenum, and one smaller ulcer (0.5 by 1 cm.) in the pyloric ring, while the rest of the stomach showed areas of hemorrhage and small ulcers. The margins of the ulcers, which were infiltrated, appeared necrotic. The ulceration in the duodenum had extended to the peritoneal coat, where there were peritoneal adhesions. The muscles contained numerous whitish streaks, especially the superficial muscles of the neck, shoulders, thorax, and diaphragm. The myocardium, which was flabby, contained a moderate number of whitish areas. Similar lesions were found in the nonstriated muscle fibers of the large and small intestines. The kidneys showed the picture of focal and ascending nephritis. There was present also suppurative conjunctivitis of the right eye, associated with hemorrhages of the sclera at the limbus.

Sections of the ulcer of the pyloric end of the stomach showed marked leukocytic infiltration and hemorrhage in its base, degeneration of the mucous glands, and beginning fibrosis (Fig. 22). Stains for bacteria showed a moderate number of diplococci in the submucosa and in the ulcerated area.

RESULTS

The details of these experiments suffice to illustrate the results obtained.

The injection of staphylococci and of Bacillus subtilis from 4, and of the yeasts from 1 of the ulcers isolated in the earlier cases, produced no lesions in the stomach, and hence were considered accidental invaders.

Cultures of streptococci which in the earlier experiments had proved able to produce ulcer when injected intravenously, failed to do so when injected into dogs fed with mixtures of meat and sharp particles of bone.

In Table 1 is given a summary of all the results following intravenous injection of streptococci from ulcer. Hemorrhage and ulcer of the mucous membrane of the stomach or of the duodenum occurred

following injection of 19 strains when first isolated in 61% and 60% respectively of 117 animals injected. This is in marked contrast to an incidence of 20% hemorrhages and 8% ulcers following injection of 180 strains of streptococci from sources other than ulcer.

It should be emphasized here that these results were not obtained during a short interval only, but that the experiments extended over a period of 3 years, were done in different localities, and at all seasons of the year. They included altogether 6 species of animals (dog, rabbit, guinea-pig, monkey, cat, and mouse).

The selective affinity for the stomach and the duodenum disappeared both after cultivation of the bacteria on artificial media for from 1 to 6 weeks and after animal passage, the incidence of ulcer dropping from 60% to 0% after cultivation and to 33% after animal passage. The strains kept on artificial media acquired greater affinity for the

TABLE 1

ELECTIVE LOCALIZATION OF STREPTOCOCCI FROM ULCER OF THE STOMACH

The Time of the Injection of Streptococci	Strains	Animals Injected	Percentage of Animals Showing Lesions in		
			Appendix	Stomach and Duodenum	
				Hemorrhage	Ulcer
When isolated	23	117	2	61	60
Later	8	22	5	5	0
After animal passage	7	39	0	23	33

appendix. The strains passed through animals acquired greater affinity for the gall-bladder and the pancreas.[43] While the affinity for the stomach was usually more marked in the streptococci from the ulcer itself than in those from the focus of infection, yet the latter had an unmistakable affinity also. In the case of recurring ulcer of the somach (Case 236) following an ulcerated tooth, the streptococcus from the pus from the sinus showed an affinity for the stomach so marked that it produced ulcer not only after intravenous, but also after intraperitoneal and intrapleural, injections.

In the case of recurring ulcer (Case 531) in which the attacks always followed tonsillitis, ulcer of the stomach followed injection of the bacteria directly from the extirpated tonsils and of the primary cultures from the tonsils, in all but 2 of 7 animals injected. Streptococci from the alveolar abscess at the apex of an extracted tooth in a patient with acute ulcer of the stomach and gastric hemorrhage, produced, on

intravenous injection, hemorrhage and ulceration of the stomach or of the duodenum in 2 dogs and in 1 of 2 rabbits injected. In another case of acute ulcer following an attack of grippe, cultures from the tonsil and from the infected area about the left lower wisdom tooth, produced a hemorrhagic ulcer in the lesser curvature 2 cm. from the pyloric ring in 2 rabbits, both of which seemed well at the time they were chloroformed, 72 hours after injection.

In some instances the strains from duodenal ulcers showed an unmistakable tendency to produce ulcer in the duodenum oftener than in the stomach (see Cases 773 and 112). The strain from the peritoneal coat of the ulcer in Case 112, not only showed this to a striking degree, but in a number of animals, the infection perforated the wall of the duodenum, and produced a localized peritonitis like that present in the patient. Some of the strains from gastric ulcer tended to pro-

TABLE 1—*Continued*

ELECTIVE LOCALIZATION OF STREPTOCOCCI FROM ULCER OF THE STOMACH

Percentage of Animals Showing Lesions in									
Gall-bladder	Pan-creas	Intes-tines	Joints	Endo-cardi-um	Peri-cardi-um	Myo-cardi-um	Muscles	Kidney	Lung
20	3	7	16	12	4	5	0	5	0
5	0	0	18	14	0	0	0	0	0
30	15	15	21	5	0	3	3	8	15

duce ulcer in the stomach oftener than in the duodenum (see Case 779). This selective localization occurred too often to be accidental. In other instances, no such definite relationship between the place of isolation and the place of localization was shown.

Either or both hemorrhage and ulcer of the stomach or of the duodenum followed injection of all the strains from ulcer in a total of 93 animals (83%). Hemorrhage occurred in the pyloric portion in 38 instances, in the fundus in 34, and in the duodenum in 20; ulcer occurred in the pyloric portion in 28, in the fundus in 32, and in the duodenum in 14. Either or both hemorrhage and ulcer followed injection of strains of streptococci from sources other than ulcer, in a total of 99 animals (26%). In these, hemorrhage occurred in the pyloric portion in 38 instances, in the fundus in 29, and in the duodenum in 27; ulcer occurred in the pyloric portion in 24, in the fundus in 14, and in the duodenum in 7. The location of the ulcer corre-

sponds to the location of the hemorrhage and the location of both lesions following injection of streptococci from ulcer and other sources is comparatively fixed, being most often in the pyloric portion, along the lesser curvature, or in the duodenum, and least often in the fundus of the stomach.

In summarizing the locations of 25 ulcers, which were disclosed from 1 to 17 weeks after the primary injection, many of which, chiefly in dogs, had taken on features typical of chronic ulcer, it was found that 12 were in the pyloric portion, 4 being along the lesser curvature, 2 in the fundus, and 7 in the duodenum. Healing ulcer, or scars of healed ulcers, were found in 7 instances, from 18 to 120 days after injections. All but 2 of these were situated in the fundus, the others in the pyloric portion.

The location of the experimental ulcers, therefore, corresponds strikingly to the location of ulcer in man, as found at autopsy and in the operating room (Mayo[44]). The duodenal ulcers occurred usually just outside (Fig. 16), and always within two inches of, the pyloric ring. In the dogs, they were found chiefly in the anterior and posterior walls. Hemorrhage and ulceration at the ampulla occurred oftener in the rabbits than in the dogs. In one such ulcer, the orifice was plugged with mucopus, and the common duct was edematous.

Severe or fatal hemorrhage occurred from the more chronic ulcers in 7 instances. Three of the ulcers were situated in the pyloric portion of the stomach and 4 in the duodenum. Four of these showed thrombosis of blood vessels in the submucosa.

In some cases, the anemia was out of all proportion to the amount of blood found in the stomach and bowel at autopsy. This indicated that repeated hemorrhages had occurred, or that a slight oozing had persisted for a long time.

The incidence of ulcer following injection of the streptococci from cholecystitis (15%), acute appendicitis (1%), rheumatic fever (18%), herpes zoster (8%), and other sources, corresponds in a general way to the incidence of ulcer in those diseases in man.

The chief difference between the lesions in the stomach or the duodenum following injection of the strains from ulcer, and those following injection of strains from other sources, was one of total incidence and degree, rather than of kind, the strains from ulcer showing by far the greater affinity for the stomach and duodenum. The lesions in both cases were due to localized infection of the mucous membrane, usually demonstrable at the time of examination.

The results given in the table were obtained without special attention to the time of injection of the bacteria in relation to the functional activity of the stomach. The fact that in a given series of animals injected with the same strain, there were one or two in which the stomach showed no lesions whatever when the stomach in all the rest showed marked lesions, indicates that the state of function is of importance in determining the localization and production of ulcer.

Colon bacilli were almost always absent in both duodenal and gastric ulcer in animals which were chloroformed. This is in accord with the fact that colon bacilli were absent in nearly all the ulcers in man excised at operation.[41]

DESCRIPTION OF THE ULCERS

In most instances, there occurs a primary lodgement and growth of bacteria, in the interstitial tissue of the glands and between the cells, followed by hemorrhage, necrosis, and ulceration. The loss of tissue usually begins in the center of the hemorrhagic infiltrated and necrotic area as early as 18 hours after injection, and spreads to the periphery. The surrounding blood vessels are congested. In some instances, the ulcer forms without a preceding hemorrhage, in circumscribed grayish swollen necrotic areas. The ulcers are deeper in the center and penetrate rapidly to the muscularis mucosa. The base in the acute ulcer is hemorrhagic, while in the more chronic type, it is clean.

Microscopically, both the circumscribed hemorrhage and the ulcer are cone-shaped, with the base of the cone at the surface and the apex at the muscularis mucosa. The streptococci lodge in the fine capillary network about the gland tubules or tissue spaces, and multiply so that in 24 or 48 hours there are often enormous numbers of streptococci at the apex of a hemorrhagic area (Figs. 15, 18, and 20). A necrotic process surrounds this area, and as the overlying mucous membrane sloughs, it carries with it most of the bacteria (Fig. 6.)

This finding explains the observations made repeatedly; namely, that the cultures from the ulcerated area often show fewer colonies than those from adjoining areas of hemorrhage (experiment on Dog 120 with streptococcus from the tooth in Case 52). The number of colonies, especially if the animal has been dead for a time, is often surprisingly small, ranging usually from relatively few to thousands. From a careful study of numerous sections and of the results of the cultures, it is certain that following the primary sloughing, the number

of streptococci in the remaining more or less healthy tissue is not usually very large, bacteria being often hard to find.

The cellular infiltration surrounding the chronic ulcers is usually not marked, but frequently extends into the submucosa, the muscular layer, and at times through the peritoneal coat. The connective-tissue formation is well advanced in some ulcers and at times extends far beyond the ulcerated area (Fig. 22). In some instances, it involves the muscular layer and peritoneal coat (Fig. 8). In the chronic ulcers, both in man and in animals, the streptococci present are few in number and are found chiefly in the areas showing cellular infiltration surrounding the necrotic process, along the supporting tissue, the gland tubules, along partition membranes, and not infrequently in the subperitoneum. There are often marked intraglandular infiltration, disintegration, and disappearance of the chief cells of the gastric tubules while the parietal cells remain unaffected (Fig. 5). This is in agreement with the findings of Korczynski and Jaworski[45] in the case of ulcer in man. Completely or partially thrombosed blood vessels have been found in or adjoining the experimentally produced ulcers in 9 instances. In 3 of these, the thrombi contained streptococci (Dog 156, Case 112, and Figs. 11 and 12).

In 4 instances only, the ulcer appeared to be secondary to a primary infection in the lymph follicles, but in none of these was the evidence entirely convincing (Fig. 23).

THE MECHANISM OF THE FORMATION OF THE ULCER

Bensley and Harvey[46] have shown that the hydrochloric acid in the normal stomach is formed on the free surface. It occurred to me that possibly the localized infection might alter the secretory activity of the cells, and that the hydrochloric acid might be formed within the cells in the depths of the mucous membrane, which would then directly become digested and the ulcer result. An attempt was therefore made to study this point by the use of indicators under the conditions given by Bensley and Harvey. I wish here to express my appreciation to Dr. Harvey for valuable aid and suggestions in the use of their technic.

The difficulties to be overcome were obviously great. The affinity of many strains for the stomach is transient. The size of the injection had to be regulated so that the amount of ulceration and general illness would not be sufficient to interfere with the appetite of the animal. The lesion had to be in the acid-secreting portion. The process had to be studied after distinct lesions had taken place, but preferably

before marked ulceration had occurred. Repeated experiments resulted in failures, but in 2 rabbits and 1 dog all necessary requirements were fulfilled. I cite only one experiment.

Rabbit 676.—Injected intravenously June 28, 1914, with the growth from 45 c.c. of an ascites dextrose tissue broth of a streptococcus (31) from ulcer in man.

June 29.—Seemed well, was fed cabbage and grass, ate heartily; killed by sudden blow on the head. Stomach removed and opened at once. The content was highly acid to litmus. The mucous membrane was washed for an instant in cold water. There was a hemorrhage with beginning ulceration in the mucous membrane of the cardiac end of the stomach (3 by 2 mm.). One-half of the ulcer was saved for cultures, the other studied at once. Bits of the hemorrhagic mucous membrane with beginning ulceration in the center, and adjoining normal mucous membrane were placed in saturated solution of cyanamin bichlorid, in salt solution, and in a solution of 1 part of neutral red to 10,000 parts of salt solution, where they were allowed to remain for a few minutes. They were then rapidly mounted on slides in the solutions, pressed flat with a cover glass, and examined.

The normal mucous membrane presented the picture described by Bensley and Harvey. There was no acid in the glands, but an abundance in the foveola (blue in cyanamin solution, red in neutral-red solution). There was no acid in the foveola in the hemorrhagic area, or in that immediately surrounding this area. The gland cells in the hemorrhagic area became acid more rapidly than the adjacent more normal cells. There was no evidence of secretion in the parietal cells.

June 30.—Cultures from blood, bile, liver, and joint fluid, were negative, while those from the ulcer showed 50 colonies of streptococci.

The results of this study indicate that the infection inhibits locally the secretory function of the gastric cells, and that the digestion of the damaged cells is due to the gastric juice formed in other portions of the stomach. The infection in the fundus is not essentially different from infection in the duodenum or in the pylorus or in other tissues.

THE STREPTOCOCCI

The streptococci isolated from the ulcers produced small, moist, nonadherent, discrete, grayish-brown or grayish-green colonies on blood (human) agar plates, and produced short chains and masses of coccus-like forms (Fig. 1), a diffuse turbidity with a flocculent sediment, and much acid in dextrose broth and ascites dextrose broth. They acidify, but usually do not coagulate, milk. They are free from capsule, are bile-insoluble and freely susceptible to phagocytosis. They do not ferment inulin and produce much acid and precipitate ascites dextrose agar. They resembled very closely those isolated in appendicitis and cholecystitis. In only one instance were there isolated

typical hemolytic streptococci from the ulcer wall, and in no instance from the lymph glands draining the ulcer.

In the primary cultures, smears from single colonies, especially from those in ascites dextrose agar, showed at times so little chain-formation and so many clumps made up of small cocci and indistinct diplococci that it was difficult to decide whether a given colony represented a mixture of streptococci and staphylococci, or a peculiar streptococcus. Subcultures on blood-agar plates or in broth usually cleared up the point.

The cultures from the supposed atrium of infection showed chiefly nonhemolyzing streptococci. In most instances, however, hemolyzing streptococci in small numbers, together with a few colonies of staphylococci, were also present, and the usual number of gram-negative cocci resembling Micrococcus catarrhalis. Injection of mixtures of hemolyzing and nonhemolyzing streptococci was usually followed by ulcer and arthritis. The former, in some instances, proved to be due to Streptococcus viridans, the latter to hemolytic streptococci. In no instance did the hemolyzing streptococcus show predilection for the stomach.

Streptococci from the most chronic ulcers produced the smallest colonies, the least amount of green on blood-agar plates, and the shortest chains in ascites dextrose broth and other liquid media. Most of the strains resembled Streptococcus faecalis (Horder). A number produced a narrow zone of hemolysis peripheral to the primary green zone. Blood corpuscles in broth cultures were usually not dissolved, or were dissolved very slowly. The strains from the two acute ulcers, as did most of the strains from the supposed atrium of infection (Fig. 2) which had affinity for the stomach, produced a larger amount of green on blood agar. With all strains tested, animal passage tended to increase the size of the colonies, and the amount of green-production. Two of the strains (from Cases 773 and 779) appeared to take on hemolytic properties in dogs during, respectively, the 5th and 6th animal passages. The changes which these streptococci underwent are in accord with those observed by me in a special study of this question several years ago.[43]

The property on which the characteristic localization depended, could be preserved best in the depth of the original cultures in ascites dextrose broth and in salt solution, containing pieces of tissue, kept in the ice chest. Cultural and other changes were often not demon-

strable as the strains lost their power to produce ulcer as a result of cultivation on artificial media.

The virulence on isolation was relatively low, as shown by the fact that intraperitoneal injection into mice of large doses of 7 strains isolated from chronic ulcer was followed by recovery in all; as shown also by the fact that 57% of the animals injected were chloroformed after they had seemingly recovered from the effects of even large doses of the culture, and that the blood in 55% was sterile at autopsy, notwithstanding the fact that many animals were examined in from 24 to 48 hours after injection. This is in sharp contrast with the results in the animals showing ulcer following injection of streptococci from sources other than ulcer. Here 91% died from the effects of the injection, and 80% showed streptococci in the blood. The limited power of the strains from ulcer to invade the blood or other structures is shown further by the fact that the cultures from the joint fluid yielded streptococci in only 22% of 40 tested, while the joint fluid in animals showing ulcer after injection with streptococci from sources other than ulcer, showed streptococci in 80% of 39 tested. The injected streptococcus was found in the bile, often in large numbers, in approximately 50% of both sets of animals, irrespective of whether or not there were lesions in the gallbladder or bile ducts. The size and moistness of the colonies, and the amount of green-production on blood agar, became greater as virulence was increased, after successive animal passages. In a number of these strains there appeared a distinct but narrow capsule. The strains from ulcer resembled in virulence and in other features those isolated by Dudgeon and Sargent[38] from the edges of perforating ulcer.

The details of the fermentative powers are reserved for a separate paper. It should be stated, however, that the fermentative powers of 12 strains in the various sugars, were tested repeatedly. The fermentative powers of the various strains were not identical and fluctuated considerably. Acid was produced in dextrose by all. Lactose was fermented in all but 6 instances. Saccharose was fermented in 14 of 20 tests. Acid was produced in raffinose in only 8 of 52 instances, in mannite in 34 of 60 tests, in salicin in 46 of 55 tests, and in inulin in only 3 of 64. The three strains which fermented inulin, produced green colonies on blood agar, and resembled pneumococci morphologically.

Altho the different strains from the ulcers and foci of infection are much alike, their fermentative and other features differ in certain

important respects. They are not sufficiently alike to warrant considering them a distinct or specific species.

GENERAL DISCUSSION

The fact that the dogs fed with mixtures of meat, sharp particles of bone, and streptococci, failed to develop ulcer, and the fact that certain persons have swallowed splinters of glass many times without developing ulcer, indicate that local injury by swallowed food, or even local invasion of bacteria from the mucous membrane is rarely, if ever, the cause of ulcer.

In the light of these experiments, the thrombosis in ulcer in man, first observed by Virchow[47] in 1853, and frequently since, must be considered retrograde and secondary to an antecedent localized infection. While it is of importance in preventing the healing of an ulcer already formed, it cannot by itself be the primary cause, because ulcer does not regularly follow obstruction of numerous small arteries,[32, 48, 49, 50, 51] not even after ligating one-third of the arteries to the stomach.[52]

The results of Turck[29] on the production of ulcer in animals by injection and feeding of colon bacilli, possibly applicable in some ulcers, in the light of these findings have little bearing on the chief problem of ulcer of the stomach and of the duodenum in man. Colon bacilli are rarely found in ulcer in man during life, and, if Turck's feeding experiments have a bearing, ulcer of the stomach should occur chiefly in persons with profound malnutrition, the result of improper and insufficient food and unsanitary surroundings.

Since streptococci from certain foci of infection in patients with ulcer tend to produce ulcer of the stomach in animals, might not the frequency of ulcer in the male sex, in certain localities, and during the winter months,[53] be best explained on the basis of a high incidence of throat and other infections? Such infections would afford opportunity for streptococci to acquire affinity for the stomach and to gain entrance into the blood stream.

The ulcers produced in my experiments, just as do spontaneous ulcers in man, tended to heal in the fundus, and to become chronic in the pyloric portion, the lesser curvature, or the duodenum. While the elective affinity of the bacteria for the gastric mucous membrane is the primary cause of the ulceration, certain contributing factors play a definite rôle in making for the chronicity of the ulcer.

The digestive action of the gastric juice has been repeatedly put forth as a cause of ulcer and as the chief factor in preventing the heal-

ing of ulcer. But this is improbable, inasmuch as recent roentgenologic studies[54, 55, 56] have shown that hyperacidity and violent spasms may be present over a period of years from causes outside the stomach without the development of ulcer. Ulceration does not occur along the segment of the stomach thrown into violent spasm directly opposite a chronic ulcer. An example of this is shown in Fig. 24, for which I am indebted to Dr. Carman. The promptness with which defects in the mucous membrane of the stomach heal after excision, after injection of corrosive chemicals, after interference with the blood supply, and after operations, shows how unimportant is the action of the gastric juice. The fact that ulcer occurs in achylia gastrica[57] also supports this view.

Some ulcers in man may be made to heal when the acidity is reduced by the administration of alkalies, as advocated especially by Sippy,[60] or by the alkaline contents of the duodenum, following gastroenterostomy.* Might not the good effect be due partly to an alkalization of the tissues throughout the body, rather than wholly to local action? The direct digestive action of the hyperacid gastric juice on the floor of the ulcer is believed to prevent the healing. If this is true, chronic ulcer should be found where this action proceeds for the longest time and is most direct; that is, in the acid-secreting portion of the stomach. This is not the case. No matter how much prolonged or increased the action of the gastric juice, the fact remains that its corrosive action must be less in the duodenum than in the stomach, and probably is appreciably less in the pyloric segment and in the lesser curvature, the common sites of both experimental and spontaneous chronic ulcers. Something with greater penetrating power than the gastric juice must first damage the cells before they can be digested.

Clinical, roentgenologic,[54] and experimental studies[3, 5, 58, 59] on the physiology of the stomach prove conclusively that ulcers along the lesser curvature, in the pylorus, and in the duodenum, are especially prone to be associated with abnormal motility of the stomach and spasm of the pylorus, resulting in delayed emptying, hypersecretion, and hyperacidity. This peristaltic unrest produces mechanical injury, necessarily greatest in the relatively fixed points where chronic ulcer occurs,[62] prevents physiologic rest, and hence serves to maintain the primary infection in the margin of the ulcer, at the same time increas-

* It should be remembered, however, that freedom from symptoms, and even absence of occult blood in the stool, are no proof that a chronic ulcer has healed; for, as Mayo states,[61] "When supposedly cured cases are operated on during the quiescent interval, the ulcer is not found to be cicatrized, but unhealed. Roentgenograms show the same thing."

ing the liability to secondary infection. This mild, but long-continued, traumatism appears to be of greater importance in preventing healing than the direct corrosive action. Infection and infiltration of connective tissue are favored, resulting ultimately in the calloused crater-like ulcer, which for mechanical reasons cannot heal, even tho the infection is reduced to a minimum or is completely overcome.

This conception is in accord with the results obtained by Bolton,[5] who showed that partial closure of the pylorus delayed the healing of ulcers produced by injections of gastrotoxic serum, but only of those that became "septic." It is in accord with Bolton's[63] more recent results in which he again showed that delayed healing of ulcer occurred chiefly in those animals in which the obstruction at the pylorus was so marked as commonly to cause death, and in those which were given abnormal concentrations of hydrochloric acid. It is not at variance with the results of Hamburger and Friedman,[3] who showed that partial obstruction of the pylorus resulting in extreme hypermotility and dilation, delayed the healing of ulcers produced by local injection of silver nitrate, particularly in the pyloric portion. It is in accord with the results of Durante,[23] who produced ulcers by ligating the splanchnic nerves. The ulcers shown by him to be chronic, present evidence of infection. If Durante had searched for bacteria, he would undoubtedly have found them, because in one of the "chronic" ulcers, I demonstrated (after the publication of his paper) not less than 50 cocci and diplococci in the depths of the tissue, which showed leukocytic infiltration; moreover no bacteria could be found in the healing ulcer from the same stomach, which showed no leukocytic infiltration.

Might not this conception best explain the etiologic relationship to ulcer of the vagotonic or neurotic state in general, as emphasized especially by Westphal and Katsch,[64] de Kock,[65] Gunderman,[66] and Eppinger and Hess?[67] Disturbed motility and spasm of the stomach and hyperacidity, occur commonly in neurotic persons.

Moreover, if lesions of the autonomic nervous system are ever a cause of ulcer, as emphasized by Durante's experiments, then it may be suggested in the light of the work by Oftedal and myself on herpes zoster,[68] and other more recent experiments, that streptococci or other bacteria or their toxic products may be the cause of the lesions in the autonomic nervous system.

In support of the view that ulcer of the stomach in the adult is due to streptococci, it should be stated that Gerdine and Helmholz[69] by the use of the same methods have not only shown that a recent epidemic

in Chicago of duodenal ulcer in infants was due to streptococci, but on re-studying the sections of the ulcers from a similar epidemic in Berlin, reported by Helmholz[70] 7 years ago, they have demonstrated streptococci in all but 4 of 14 ulcers available.* Furthermore, in a study of the etiology of spontaneous ulcer of the stomach in dogs, calves, cattle, and sheep, in conjunction with Dr. Dart and Dr. Henderson (as yet unpublished), it appears that ulcer in these animals also is due commonly to a circumscribed streptococcal infection.

The occurrence of acute ulcer of the stomach and exacerbations of the symptoms in chronic ulcer in connection with foci of infection; the improvement in symptoms following removal of foci of infection; and the development of new ulcers after excision of ulcer in patients in whom chronic suppurating foci have not been removed—all strongly suggest the etiologic relation between remote foci of infection and ulcer. None of these observations, however, proves the etiology of the ulcer. The demonstration of streptococci in foci of infection in patients with ulcer and in the ulcers themselves, and the fact that they localize in the stomach in animals, furnish what seems to me to be the final proof of the etiology.

The conditions under which streptococci acquire affinity for various organs,[68, 71, 72, 73, 74] are still obscure, but of the existence of this affinity of streptococci in diseases, there is no question. The fact that in some instances streptococci were isolated from relatively insignificant foci of infection, and the fact of their presence in patients with ulcer over a long period suggest, as I have already pointed out,[42] "that differences in the host may afford the peculiar type of reaction or that the individual harbors a particular form of focus of infection, which is favorable for bacteria to acquire the various elective properties." These observations suggest strongly that while removal of evident foci of infection is important, cure should not always be expected.

The periodic occurrence of exacerbations in symptoms followed by quiescent intervals in chronic ulcer would seem to be best explained on the basis of infection, the former being due to a lighting up of the dormant infection or to re-infection from a focal source when immunity is low and the latter to quiescence of the infection, the result of heightened local or general immunity.

* One of the strains from a duodenal ulcer in an infant isolated by them, resembled very closely the strains isolated from ulcers in adults by Sanford and myself. This strain localized electively in the stomach of rabbits and dogs, producing ulcer, which proved to be due to local infection after intravenous injections made by Gerdine, by Hardt, and by myself. Re-injection again produced ulcer.

SUMMARY

The ulcers produced by the injection of streptococci resemble those in man in location, in gross and microscopic appearance, and in that they tend to become chronic, to perforate, and to cause severe or fatal hemorrhage.

Streptococci having a characteristic affinity, for the stomach and the duodenum, have been repeatedly isolated from various foci of infection in patients with ulcer and from the ulcers themselves. They tend to disappear from the circulation and do not commonly produce marked lesions otherwise. They have been isolated from ulcers in animals, and ulcer has again been produced on their re-injection. Filtrates of these cultures show no special tendency to produce ulcer. The necessary requirements have been fulfilled to warrant the conclusion that the usual ulcer of the stomach and of the duodenum in man is primarily due to a localized hematogenous infection of the mucous membrane by streptococci.

BIBLIOGRAPHY

1. Quincke and Dättwyler: Cor.-Bl. f. schweiz. Aerzte, 1875, p. 101. Deutsch. med. Wchnschr., 1882, 6, 79. Quoted by Ewald, Diseases of the Stomach, 1902, p. 382.
2. Becker: Berl. klin. Wchnschr., 1887, 24, p. 369. Quoted by Ewald, Diseases of the Stomach, 1902, p. 384.
3. Friedman and Hamburger: Jour. Am. Med. Assn., 1914, 63, p. 380.
4. Licini: Beitr. z. klin. Chir., 1912, 79, p. 462.
5. Bolton: Ulcer of the Stomach, 1913, p. 59.
6. Cohnheim: Lectures on General Pathology, 1890, 3, p. 879.
7. Schridde: Verhandl. d. deutsch. path. Gesellsch., 1907, 11, p. 234. Quoted by Bolton, l. c., p. 78.
8. Rehfuss: Univ. Penn. Med. Bull., 1909, 22, p. 105.
9. Smith: Jour. Med. Research, 1914, 30, p. 147.
10. Sellards: Arch. Int. Med., 1909, 4, p. 502. Abstr. Jour. Am. Med. Assn., 1909, 53, p. 24.
11. Elliott: Quart. Jour. Med., 1914, 7, p. 119. Abstr. Jour. Am. Med. Assn., 1914, 62, p. 576.
12. Friedman: Jour. Med. Research, 1915, 32, p. 287.
13. Enriquez and Hallion: Compt. rend. Soc. de biol., 1893, 5, p. 1025. Quoted by Bolton, l. c., p. 61.
14. Rosenau and Anderson: Jour. Infect. Dis., 1907, 4, p. 1.
15. Gioffi: Quoted by Pende, l. c.
16. Pende: Fisiopatologia dell' apparte parasimpatico, 1906.
17. Gibelli: Pathologica, 1909, p. 131.
18. Finzi: Virchow's Arch. f. path. Anat., 1913, 214, p. 413.
19. Mann: Jour. Exper. Med., 1916, 23, p. 203.
20. Elliott: Jour. Physiol., 1914, 49, p. 38.
21. Kawamura: Deutsch. Ztschr. f. Chir., 1911, 109, p. 540.
22. Vedova: Suppl. Policlinico, 1900, 6, p. 1153.

23. Durante: Pathologica, 1912-13, 5, p. 631. Surg., Gynec. and Obst., 1916, 22, p. 399.
24. Ewald: Klinik der Verdauungskrankheiten, 1890-93, 1, p. 122. Quoted by Ewald, 1, c., p. 382.
25. Charrin and Ruffer: Bull. Soc. anat. de Paris, 1889, 3, p. 18. Quoted by Bolton, 1. c., p. 61.
26. Chantemesse and Widal: Bull. de l'Acad. de méd de Paris, 1888, 14, p. 522. Quoted by Bolton, 1. c., pp. 61, 63.
27. Wurtz and Leudet: Arch de méd. exper. et d'anat. path., 1891, 3, p. 485. Quoted by Bolton, 1. c., p. 94.
28. Rodet and Zaïdmann: Compt. rend. Soc. de biol., 1900, 52, p. 1007.
29. Turck: Brit. Med. Jour., 1907, 1, p. 922, and other papers.
30. Steinharter: Lancet-Clinic, 1914, 111, p. 88. Boston Med. and Surg. Jour., 1913, 169, p. 81.
31. Lebert: Traité d. anat. path., 1857, 1, p. 537. Quoted by Bolton, 1. c., p. 61.
32. Cohn: Klinik der embolischen Gefässkrankheiten, 1860, p. 523.
33. Letulle: Bull. et mém. Soc. méd. d. hôp. de Paris, 1888, 5, p. 360. Quoted by Bolton, 1. c., p. 18.
34. Bezançon and Griffon: Bull. et mém. Soc. anat. de Paris, 1899, 1, p. 409. Quoted by Bolton, 1. c., p. 62.
35. Dieulafoy: Textbook of Medicine, 1902, p. 679.
36. Ewald: Diseases of the Stomach, 1902, pp. 183, 391.
37. Boettcher: Dorparter Med. Ztschr., 1874, 5, p. 148. Quoted by Bolton, 1. c., p. 60.
38. Dudgeon and Sargent: The Bacteriology of Peritonitis, 1905, p. 58.
39. Hutyra and Marek: Spezielle Pathologie und Therapie der Haustiere, 1913, 2, p. 331.
40. Rosenow: Jour. Am. Med. Assn., 1913, 61, p. 1847.
41. Rosenow and Sanford: Jour. Infect. Dis., 1915, 17, p. 219.
42. Rosenow: Jour. Am. Med. Assn., 1915, 65, p. 1687.
43. Rosenow: Jour. Infect. Dis., 1914, 14, p. 1.
44. Mayo: Boston Med. and Surg. Jour., 1914, 170, p. 149.
45. Von Korczynski and Jaworski: Deutsch. Arch. f. klin. Med., 1891, 47, p. 586. Quoted by Ewald, 1. c., p. 194.
46. Bensley and Harvey: Tr. Chicago Path. Soc., 1913, 9, p. 14.
47. Virchow: Virchow's Arch. f. path. Anat., 1853, 5, p. 362. Quoted by Bolton, 1. c., p. 396.
48. Möller: Ergebn. d. inn. Med. u. Kinderh., 1911, 7, p. 520.
49. Pavy: Guy's Hosp. Rep., 1867, 13, p. 494. Roy. Soc. Proc., 1863, p. 386. Quoted by Bolton, 1. c., p. 70.
50. Roth: Virchow's Arch. f. path. Anat., 1869, 45, p. 300.
51. Litten: Virchow's Arch. f. path. Anat., 1875, 63, p. 289. Quoted by Trotter, Embolism and Thrombosis, 1913.
52. Litthauer: Virchow's Arch. f. path. Anat., 1909, 195, p. 317. Quoted by Bolton, 1. c., p. 128.
53. Moynihan: Duodenal Ulcer, 1910, pp. 106, 251.
54. Carman: Am. Jour. Roentgenol., 1914, 1, p. 233.
55. Rieder: Verhandl. d. deutsch. Kong. f. inn. Med., 1912, 29, p. 17.
56. Holzknecht and Luger: Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1913, 26, p. 669.
57. Eusterman: Jour. Am. Med. Assn., 1915, 65, p. 1500.
58. Cannon: The Mechanical Factors of Digestion, 1911.

59. Carlson: New York Med. Jour., 1915, 102, p. 1004. Also numerous recent publications in the Am. Jour. Physiol.
60. Sippy: Jour. Am. Med. Assn., 1915, 64, p. 1625.
61. Mayo: Jour. Am. Med. Assn., 1915, 65, p. 1069.
62. Stromeyer: Beitr. z. path. Anat. u. z. allg. Path., 1912, 54, p. 1.
63. Bolton: Jour. Path. and Bacteriol., 1915, 20, p. 133.
64. Westphal and Katsch: Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1913, 26, p. 391.
65. De Kock: Nederl. Tijdschr. v. Geneesk, 1913, 2, p. 449.
66. Gundermann: Beitr. z. klin. Chir., 1914, 90, p. 1.
67. Eppinger and Hess: Samlung klinischer Abhandlungen über Pathologie und Therapie der Stoffwechsel und Ernährungstörungen, 1910, Vols. 9 and 10.
68. Rosenow and Oftedal: Jour. Am. Med. Assn., 1915, 64, p. 1968.
69. Gerdine and Helmholz: Am. Jour. Dis. Child., 1915, 10, p. 397.
70. Helmholz: Arch. Pediat., 1909, 26, p. 661.
71. Rosenow: Jour. Infect. Dis., 1915, 16, p. 240.
72. Rosenow: Jour. Am. Med. Assn., 1914, 63, p. 1835.
73. Rosenow: Jour. Infect. Dis., 1915, 16, p. 367.
74. Irons, Brown, and Nadler: Jour. Infect. Dis., 1916, 18, p. 315.

EXPLANATION OF PLATES

PLATE 5

FIG. 1. Smear from a 24-hour ascites-dextrose-broth culture of the streptococcus isolated from a duodenal ulcer in man (Case 773). Gram-Weigert stain. × 1,200.

FIG. 2. Smear from a 24-hour ascites-dextrose-broth culture of the streptococcus isolated from an infected tooth in a patient with ulcer of the stomach. The smear was made at the time that the strain was proved to have affinity for the stomach in animals (Case 52). Gram stain. × 1,200.

PLATE 6

FIG. 3. Multiple hemorrhages, necroses, and ulcerations of the mucous membrane of the stomach of Dog 42, Case 779, 4 days after an intravenous injection of a streptococcus isolated from a gastric ulcer in man and passed through one animal. Natural size.

FIG. 4. Section through the area of the stomach at "a" in Fig. 3, showing the sloughing mucous membrane, the marked hemorrhage, leukocytic infiltration, the poorly staining cells, and the aggregations of leukocytes in the dilated blood vessels in the submucosa. Hematoxylin and eosin. × 50.

PLATE 7

FIG. 5. A portion of the infiltrated and necrotic mucous membrane of the ulcer shown in Fig. 4, under higher magnification. Marked disintegration and disappearance of the chief cells, leukocytic infiltration, and relatively normal appearance of the parietal cells. Hematoxylin and eosin. × 400.

FIG. 6. Photomicrograph of a mass of diplococci and streptococci in the sloughing portion of the ulcer shown in Fig. 4. Gram-Weigert stain. × 1,000.

PLATE 8

FIG. 7. Chronic ulcer of the duodenum in Dog 37, Case 773, 14 weeks after intravenous injection of a streptococcus from an excised ulcer of the duodenum in man. Natural size.

FIG. 8. Section of the ulcer shown in Fig. 7. Invasion of the muscular coat by connective tissue at "a" and peritoneal adhesions at "b." Hematoxylin and eosin. × 80.

FIG. 9. Diplococci in the margin of the ulcer shown in Fig. 8. × 1,000.

PLATE 9

FIG. 10. Ulcer of duodenum at "a" in Dog 156 (Case 112) 18 days after intravenous injection of a streptococcus from the peritoneal coat of an ulcer in the duodenum in man (Case 112). Natural size.

FIG. 11. Section of the ulcer in the duodenum shown in Fig. 10. Ragged base, poorly staining connective-tissue stroma, moderate leukocytic infiltration, thrombosed vessels (b), and a large number of leukocytes in the thrombi. Hematoxylin and eosin. × 120.

FIG. 12. Photomicrograph of two diplococci found in the thrombosed vessel at "a" in the ulcer shown in Fig. 11. Gram-Weigert stain. × 1,000.

PLATE 10

FIG. 13. Streptococci in the peritoneal coat of a perforating ulcer of the stomach in a rabbit (R652) 35 days after intravenous injection of the streptococcus isolated from a lymph-gland draining a perforating ulcer of the duodenum in man (Case 947). Gram-Weigert stain. × 1,200.

FIG. 14. Marked ulceration of the stomach in a guinea-pig (P12) 24 hours after intravenous injection of a streptococcus from a suppurating frontal sinus in a man with ulcer of the stomach (Case 213).

FIG. 15. Chains of diplococci in the margin of the ulcerated mucous membrane shown in Fig. 14. Gram-Weigert stain. × 1,000.

PLATE 11

FIG. 16. Hemorrhage in the duodenum in a rabbit (R792) 48 hours after intravenous injection of a streptococcus from the tonsil in a patient with arthritis deformans and probable ulcer of the stomach (Case 163). Natural size.

FIG. 17. Ulcer of the mucous membrane of the stomach in a rabbit (R787) 3 days after intravenous injection of an emulsion of the tonsils from a case of arthritis deformans with symptoms suggesting ulcer of the stomach (Case 163). Note the dark radiating areas at "b" and the apex of the ulcerated area shown at "a." Hematoxylin and eosin. × 60.

FIG. 18. A higher magnification of the dark radiating area at "b" in Fig. 17, showing an enormous number of streptococci. × 1,200.

PLATE 12

FIG. 19. Section of the wall of the stomach in a rabbit (R68) showing wedge-shaped area of leukocytic infiltration, hemorrhage, and beginning ulceration, 48 hours after intravenous injection of a streptococcus isolated from the tonsil in herpes zoster and passed through one animal. Hematoxylin and eosin. (Case 281.) × 80.

FIG. 20. Streptococci at the apex of the wedge-shaped area shown in Fig. 19. Gram-Weigert. × 1,200.

PLATE 13

FIG. 21. Section of an ulcer of the stomach in a dog (D22) 12 days after intravenous injection of a streptococcus from rheumatism. Note its wedge shape and the round-cell infiltration at "a" between the necrotic and more normal tissue. Hematoxylin and eosin. × 60.

Fig. 22. Section through the base of a large ulcer in the duodenum in Dog 25, Case 531, 19 days after intravenous injection of a streptococcus isolated 11 years previously as a pneumococcus. Marked hemorrhage, leukocytic infiltration, and connective-tissue formation. Neutral gentian. × 60.

FIG. 23. "Follicular" ulcer of the pylorus of a dog following repeated injections of a streptococcus from a lymph gland at the pole of the thyroid in exophthalmic goiter. There is marked hemorrhage in the submucosa and surrounding the lymph follicle, infiltration, necrosis, connective-tissue formation; the muscular layer is normal. Neutral gentian. × 40.

PLATE 14

FIG. 24. Woman aged 52 years. Small bulb-like projection from lesser curvature in pars media, at "A," which is the crater of a penetrating ulcer. At "B" is shown the cramp-like constriction (incisura) of the circular muscle fibers. Operative findings: Gastric ulcer high on the lesser curvature. Moderate hour-glass contraction (Carman—Case A—107649).

Plate 5

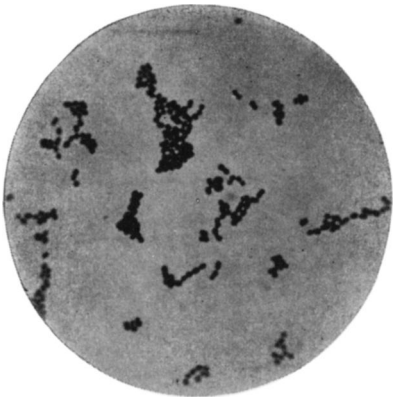

Figure 1

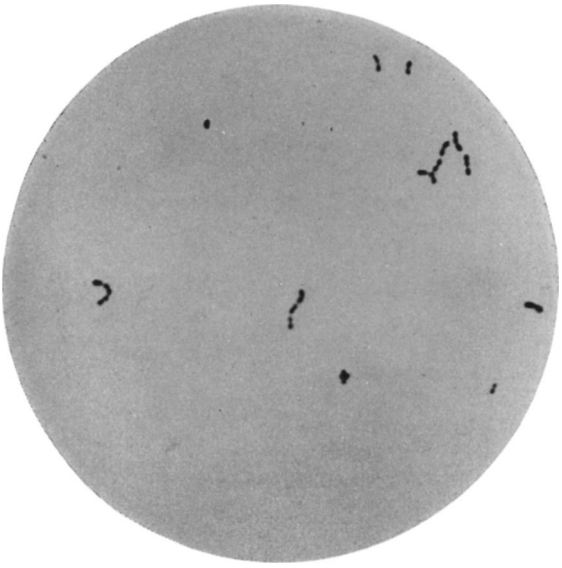

Figure 2

Plate 6

Figure 3

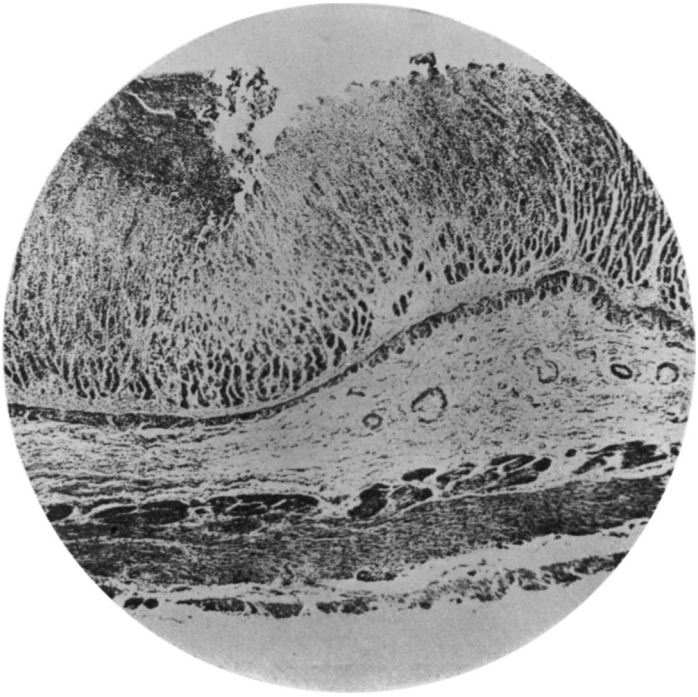

Figure 4

Plate 7

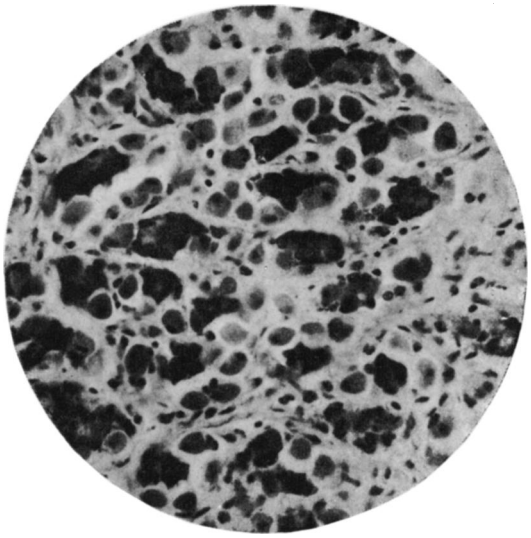

Figure 5

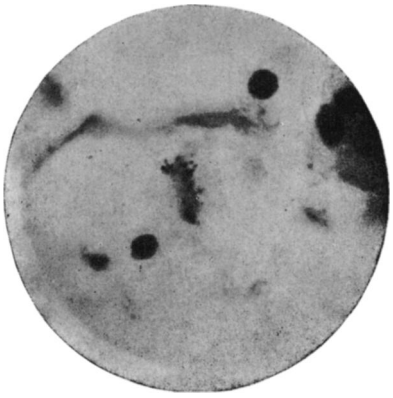

Figure 6

Plate 8

Figure 7

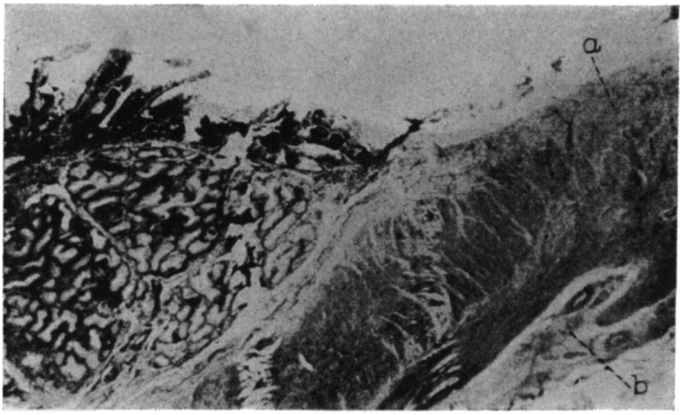

Figure 8

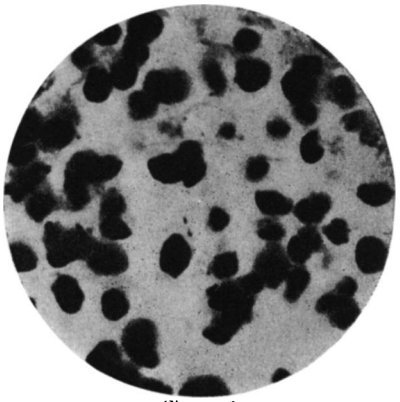

Figure 9

Plate 9

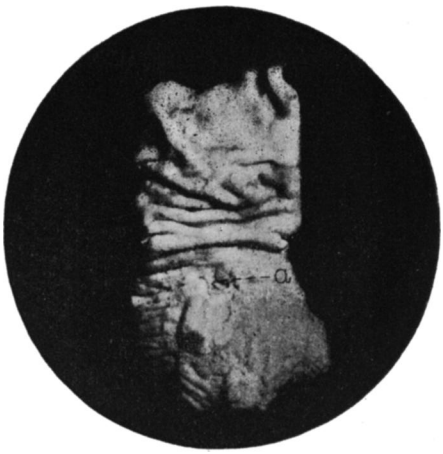

Figure 10

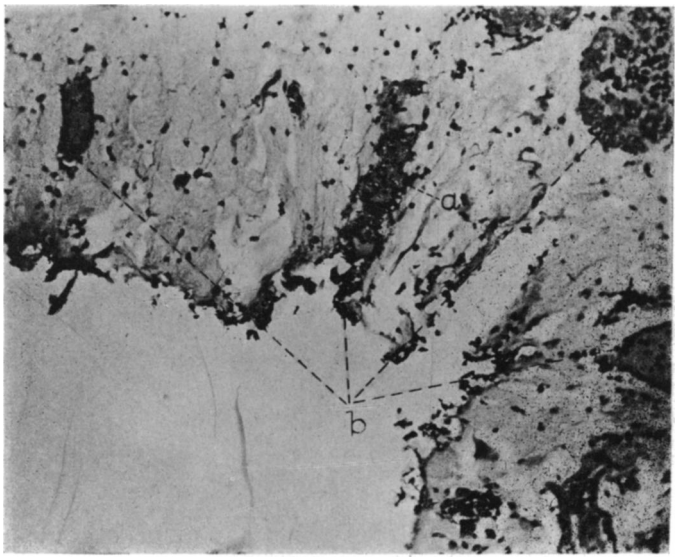

Figure 11

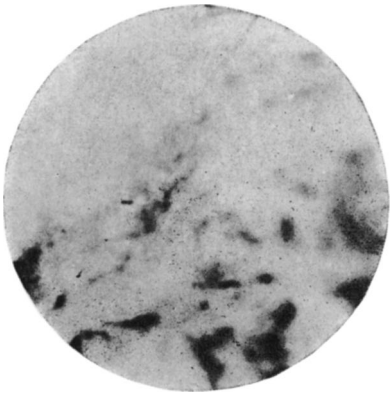

Figure 12

Plate 10

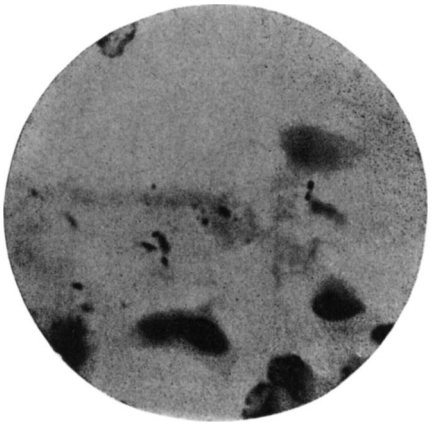

Figure 13

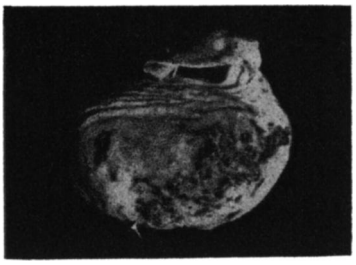

Figure 14

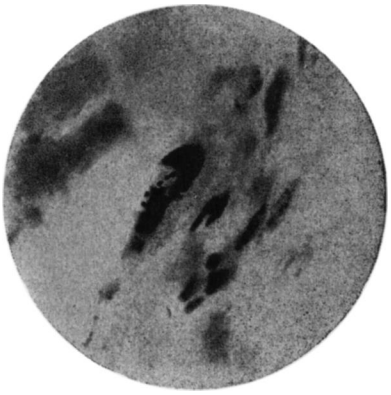

Figure 15

PLATE 11

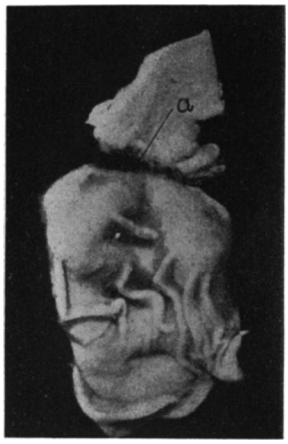

Figure 16

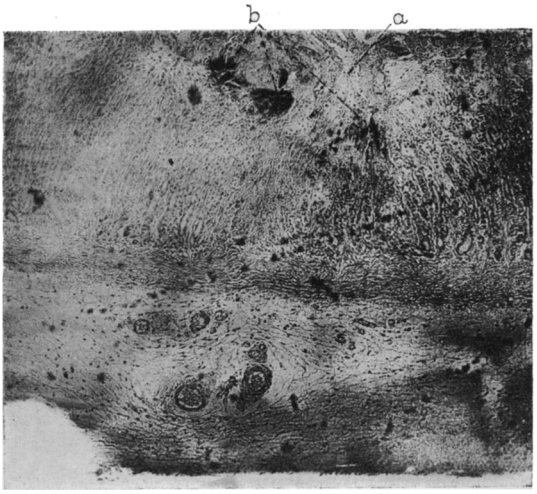

Figure 17

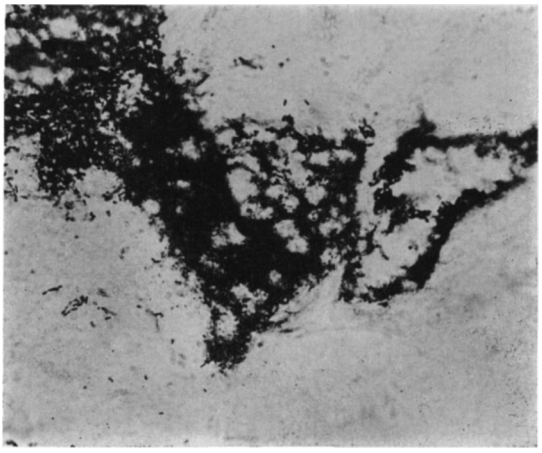

Figure 18

Plate 12

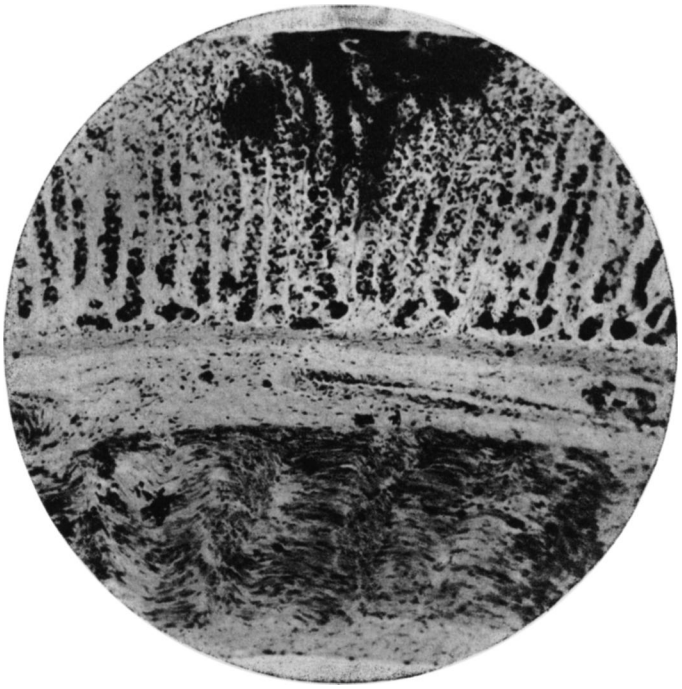

Figure 19

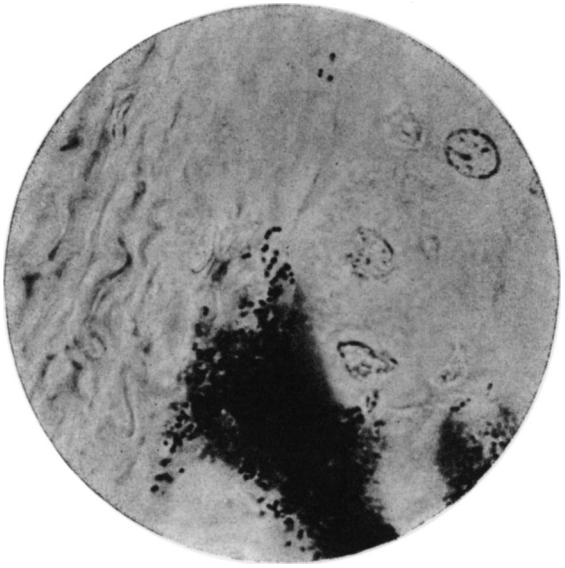

Figure 20

PLATE 13

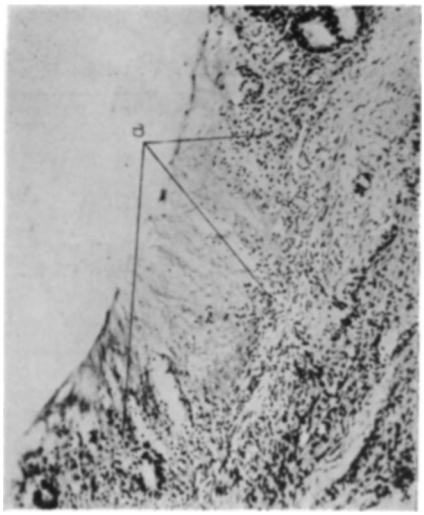

Figure 21

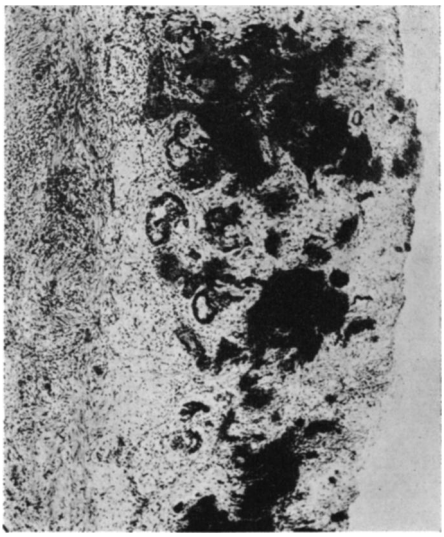

Figure 22

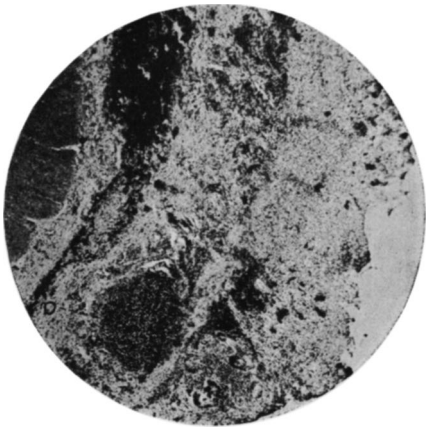

Figure 23

PLATE 14

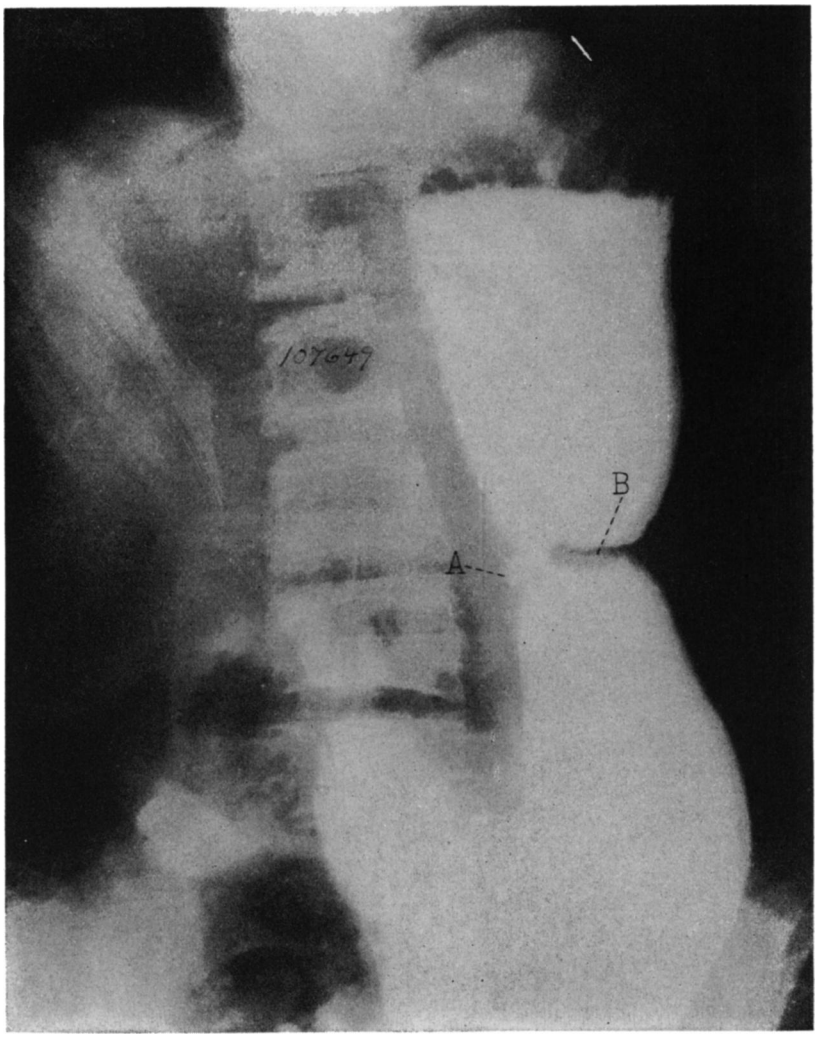

Figure 24